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10/528,377	01/04/2006	Jeffrey S. Glenn	STAN-316	7561

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,377	GLENN ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *11-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of Group I, and species (B) in the reply filed on August 7, 2007 is acknowledged. The traversal is on the ground(s) that the claims, as amended, do share a common special technical feature over the prior art. This is not found persuasive. With respect to Group III, it is noted that the claims of this Groups are drawn to polynucleotides encoding an HCV NS4B protein with reduced nucleotide binding activity. Such a polynucleotide would have been obvious over the teachings of the WO 99/01582 reference cited in the restriction requirement (see, page 16, teaching the expression of NS4B from a polynucleotide, and the expression of a NS4B lacking a nucleotide binding motif). Thus, Group III does not share a common special technical feature with Groups I, II, and IV.

With respect to Groups II and IV, it is noted that the NBMs identified in Figure 1C of the application are homologous to the NBM disclosed on page 13 of the WO reference. Because the reference and the present application identify the same sequences as ATP and GTP binding motifs, and as the reference also teaches the identification of compounds that inhibit the activity of this motif, treatments using such compounds would inherently perform the same function as the methods of Groups II and IV. See also, Einav et al., J Virol 78:11288-95, at 11294 (indicating that GTPases can hydrolyze other nucleotides, and that compounds effective against

NS4B polymerase activity may also be useful for inhibiting GTPase activity). Thus, these Groups do not have a special technical feature over the prior art.

The fact that to WO does not provide any explicit teachings regarding GTPase activity does not demonstrate that the reference fails to provide teachings that inherently break unity among the present claims. Because these groups do not have or share a common special technical feature over the art, Unity of invention is not present and the Applicant's arguments in traversal of the rejection are therefore not found persuasive. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 11-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 7, 2007.

4. Claims 1-10 are under consideration.

Drawings

5. The drawings are objected to because

The description of Figure 8 indicates that there should be two sets of bars, one white and the other hatched. However, all of the bars presented in the Figure are white. It is therefore not clear which bars represent the binding of GST and RNA verses GST-NS4B and RNA in the presence GTP or the analog. Because the teachings on pages 39-40 indicate that the taller bars should be the hatched bars, adding the hatched marks to these bars would not be considered new matter.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step for correlating the effect of the candidate agent on the activities of the NS4B polypeptides (and the effects seen in the additional assays) with the agent's status as an antiviral agent. For example, in claim 1, it is suggested that the additional

language "wherein, if the presence of the agent results in a reduction of the GTPase activity relative to the activity seen in the absence of the agent, the candidate agent is identified as an antiviral agent."

8. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim purports to further define claim 1. Claim 1 reads on a method involving the determination as to whether a test compound affects the GTPase activity of an NS4B polypeptide. It is known in the art that GTPase activity is the hydrolysis of GTP into GDP. Claim 4 requires that the method of claim 1 comprising determining the affect of the compound on the ability of the protein to hydrolyze GTP. Because GTPase activity is the hydrolysis of GTP, it is not clear how claim 4 is further limiting to claim, or how the metes and bounds of this claim vary from those of claim 1.

Clarification is required. It is suggested that claim 4 be deleted.

9. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is drawn to the method of claim 1, wherein the method further comprises "determining an effect on an RNA binding activity of said polypeptide." The claim is rejected because it is not clear what is meant by reference to "an RNA binding activity" of the polypeptide. In particular, it is not clear if the claim requires only that the determination involve determining the effect on the ability of the polypeptide to bind RNA, or if the claim requires a

determination as to effect of the test compound on an activity of NS4B that involves RNA-binding (e.g., RNA polymerase activity). Clarification is required.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1 and 3-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There are two grounds to this rejection. First, each of the claims is rejected for exceeding the scope for which adequate descriptive support has been provided because the application demonstrates possession of only one species of the claim genus (showing only that the HCV NS4B protein binds RNA or GTP, and has GTPase activity). Secondly, claim 5 is also rejected because the application does not provide descriptive support for methods of screening for "an RNA binding activity," as the application has disclosed only the ability of the protein to bind RNA, and not what activities the protein is performing that involves such RNA binding.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

With respect to the first basis of rejection, it is noted that the examples provided in the present application relate only to the HCV NS4B protein. The application provides no teachings or evidence that the GTPase and RNA-binding shown with respect to the HCV NS4B protein are similarly present with any NS4B, or any flaviviral NS4B protein. Moreover, a search of the prior art failed to provide any indication that those in the art would have expected all of the NS4B proteins to share such activities. In addition to the lack of multiple examples of NS4B proteins that share the required activities, it is noted that the application also fails to show that each of such proteins share any non-functional features that correlate to the presence of such activities in each of the NS4B proteins (e.g., there is no identification of similar GTP or nucleotide binding motifs in other NS4B proteins in the application).

It is noted that post-filing teachings in the art indicate that NS4B proteins of Flaviviruses share certain other topological features. Umareddy et al., J Gen Virol 87: 2605-14 (page 2605, right column). However, the art also provides some evidence of uncertainty as to whether the

activities of NS4B proteins are shared among the flaviviruses. ID. at page 2605 (noting in the right column that the various NS4B proteins have significant sequence divergence), and page 2606 (noting in the right column that while the NS4B protein was found in the replication complex of some viruses, such could not be confirmed for others). Thus, the teachings in the art fail to demonstrate that those in the art would have accepted the teachings of the present application with respect to the HCV NS4B as a demonstration that the Applicant was in possession of the claimed methods with respect to all NS4B proteins.

In addition to the rejection above, claim 5 is also rejected because the application does not provide adequate support for methods of determining the effect of candidate agents on "an RNA binding activity of" the NS4B polypeptide. This claim is drawn to a method of identifying an anti-viral compound by determining the effect of the compound on an NS4B polypeptide, and further comprising "determining the effect [of the candidate agent] on an RNA binding activity of said polypeptide." In support of this limitation, the application demonstrates that HCV NS4B binds to RNA. However, the application has provided no guidance as to what activity the polypeptide is performing that involves such RNA-binding. Absent knowledge of the nature of this activity, there is inadequate information to demonstrate possession by the Applicant of a method for measuring the effects of a test compound on an RNA-binding activity of the polypeptide because those in the art would not know what activity to screen for.

In addition to the limited information in the present application as to what RNA-binding activities the NS4B polypeptides may be performing, it is noted that the teachings in the art indicate that the while the NS4B protein is involved with and required for Flaviviral replication,

the art indicates that the role that this protein plays is not clear. See e.g., Umareddy, at page 2605, right column; and Lindström et al., Virus Res 121: 169-78 (esp. abstract, and 169 right column). Thus, in view of the lack of any indication in the present application as to what the RNA-binding activities of the NS4B protein are (other than simple RNA binding), and the teachings in the art indicating such activities of the protein were not known, the present claim is rejected as lacking adequate written description support.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Vecchio et al. (WO 99/01582- of record in the April 2006 IDS) in view of the teachings of Jin et al. (Arch Biochem Biophys 20:47-53), Kadaré et al. (J Virol 70:8169-74), and Rodriguez et al. (JBC 268:8105-10). These claims read on a method for the identification of an anti-viral agent through the identification of agents that inhibit the GTPase activity of the HCV NS4B protein.

Del Vecchio teaches that the NS4B protein of the HCV virus is an ATPase, and that the ATP-binding activity is found in the consensus sequence GXXGXGKXXXXXL. Abstract, page 13. The reference also teaches the identification of compounds that inhibit the ATPase activity as potential anti-HCV agents. Pages 16-17. However, the reference does not teach or suggest that the NS4B protein also has GTPase activity.

Jin teaches that the NTPase of the HCV NS3 protein has the ability to act on both ATP and GTP. Jin also indicates that this activity is a potential target for antiviral agents. Page 53. Each of Kadaré and Rodriguez teach that proteins from other viruses, which comprising sequences with similar nucleotide binding motifs to the motif identified in Del Vecchio, were also able to act on both ATP and GTP. Kadaré, abstract; and Rodriguez, abstract, and page 8105. In view of these teachings, those of ordinary skill in the art would have had a reasonable expectation that the HCV NS4B protein would also have GTPase activity, and that this activity would similarly be a target for anti-HCV agents. It would therefore have been obvious to those of ordinary skill in the art to have screened for HCV antiviral agents targeting NS4B GTPase activity in a similar manner to that described by Del Vecchio with respect to the ATPase activity.

Because the NS4B protein would be required to bind to the nucleotide in order to act on it, it would have been obvious to those in the art to determine the ability of test compounds to inhibit nucleotide (including GTP) binding as a means for assaying or confirming the ability of the compound to inhibit GTPase activity.

The combined teachings in the art therefore render the claimed invention obvious.

14. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Vecchio in view of Jin, Kadaré, and Rodriguez as applied to claims 1-4 above, and further in view of Morouianu et al. (PNAS 92:4318-22). These claims read on the methods of claim 1, wherein the compound to be tested in a non-hydrolysable nucleotide analog.

The teachings of Del Vecchio, Jin, Kadaré, and Rodriguez have been described above. While these reference suggest the identification of antiviral agents through identification of

compounds that inhibit NS4B GTPase activity, the references do not specifically teach or suggest embodiments wherein the compounds to be tested are non-hydrolysable nucleotide analogs.

However, Morouianu indicates that non-hydrolysable nucleotide analogs were capable of inhibiting the activity of another GTPase protein. It would therefore have been obvious to those of ordinary skill in the art to have screened such compounds for the ability to inhibit the NS4B GTPase activity. The combined teachings of these references therefore render the claimed methods obvious.

15. Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Vecchio in view of Jin, Kadaré, and Rodriguez as applied to claims 1-4 above, and further in view of Wimmer et al. (U.S. 2002/0098202). These claims read on the methods described above, further comprising a determination as to the effect of the compound on HCV replication, particularly where the testing includes the use of an HCV replicon and the replication is measured in a Huh7 cell.

The teachings of Del Vecchio, Jin, Kadaré, and Rodriguez have been described above. While the teachings of these references render obvious the identification of potential HCV inhibitors through identification of NS4B GTPase inhibitors, the references do not teach or suggest the use of HCV replicons to do so. However, Wimmer teaches HCV replicons, cells, including Huh7 cells, comprising such replicons, and the use of such for screening for anti-HCV compounds. See e.g., abstract, and pages 2, 4 (esp., paragraph [0056]), and 5 (esp., paragraph [0066]). From these teachings, it would have been obvious to those of ordinary skill in the art to use such methods as a further means of testing the anti-HCV activity of compounds identified in

the methods suggested by the teachings of Del Vecchio, Jin, Kadaré, and Rodriguez as described above. The combined teachings of these references therefore render the claimed methods obvious.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Z. Lucas/
Patent Examiner, AU 1648